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Original Research Article

Atypical Bilirubin Derangement in Organophosphorus Poisoning: A Case Series of Four Distinct Biochemical Patterns

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Abstract:

Background: Organophosphate (OP) poisoning typically manifests with cholinergic crisis due to acetylcholinesterase inhibition. Hepatic dysfunction is occasionally reported; however, significant hyperbilirubinemia—especially with distinct hemolytic and hepatocellular patterns—is uncommon and underrecognized.

Case Series: We report a series of four patients with acute organophosphate poisoning following ingestion of a combination pesticide containing chlorpyrifos and cypermethrin, all presenting with classical cholinergic features and markedly reduced serum cholinesterase levels. Notably, all cases demonstrated hyperbilirubinemia with varying underlying mechanisms.

Among them, one patient exhibited predominantly indirect hyperbilirubinemia suggestive of hemolytic pattern, supported by laboratory features consistent with hemolytic pathology. Another patient developed direct hyperbilirubinemia with significantly elevated transaminases (AST, ALT), indicating hepatocellular injury. Two additional cases demonstrated similar bilirubin derangements, reinforcing the association between organophosphate toxicity and atypical bilirubin metabolism disturbances.

Discussion: While mild hepatic enzyme elevation has been described in OP poisoning, significant bilirubin abnormalities—particularly hemolytic patterns—are rare. Proposed mechanisms include oxidative stress-induced erythrocyte damage leading to hemolysis, direct hepatotoxic effects of chlorpyrifos, and possible synergistic toxicity from co-formulated pyrethroids such as cypermethrin. Recognition of these atypical patterns is crucial, as they may influence monitoring strategies and clinical management.

Conclusion: This case series of four patients demonstrates that organophosphorus poisoning may produce four biochemical pattern of bilirubin derangement: (1) predominantly hemolytic pattern, (2) hepatocellular pattern, (3) cholestatic pattern, and (4) mixed hepatocellular–cholestatic pattern. These atypical patterns extend beyond the classical cholinergic manifestations of organophosphorus poisoning and emphasize the importance of serial liver function assessment and serum cholinesterase monitoring. Early recognition of the underlying mechanism may facilitate appropriate evaluation, avoid unnecessary investigations, and improve clinical management and prognosis.

Keywords: Organophosphorus poisoning, Chlorpyrifos, Cypermethrin, Hyperbilirubinemia, Toxic hepatitis, Hemolysis, Cholinesterase.

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Introduction

One of the most widely used pesticides in the world, organophosphorus chemicals continue to cause significant morbidity and mortality, especially in rural areas. Acute organophosphorus poisoning is still a frequent reason for emergency visits and ICU admissions in India and other low and middle income countries. Chlorpyrifos is commonly used for agricultural pest management and is regularly linked to poisoning incidents. It is generally manufactured in conjunction with cypermethrin [1].

The principal mechanism of acute organophosphate toxicity is inhibition of acetylcholinesterase, resulting in accumulation of acetylcholine at cholinergic synapses. As a result, in addition to nicotinic symptoms like muscle fasciculations, weakness, and respiratory compromise, patients usually exhibit muscarinic symptoms including salivation, lacrimation, bronchorrhea, miosis, vomiting, and diarrhoea. Confusion, convulsions, and coma are possible outcomes of central nervous system involvement [2].

Hepatic symptoms have not received as much research attention as neurological and respiratory problems. Liver enzyme levels have been shown to temporarily rise after exposure to organophosphorus in both experimental and clinical settings. Oxidative stress, lipid peroxidation, mitochondrial malfunction, the release of inflammatory cytokines, and direct hepatocellular damage are some of the suggested processes. However, hyperbilirubinemia that is clinically relevant is rare and frequently disregarded during acute care [3].

There are various ways that organophosphorus poisoning might result in hyperbilirubinemia. Conjugated or mixed hyperbilirubinemia can arise from hepatocellular damage that affects bilirubin metabolism and excretion. On the other hand, hemolysis and primarily indirect hyperbilirubinemia might result from oxidative damage to erythrocytes. Although it is infrequently reported, cholestatic damage has also been suggested. It is critical to identify these unique biochemical abnormalities since they can resemble biliary disease, hemolytic disorders, or viral hepatitis [4].

The present case series describes four patients with acute chlorpyrifos–cypermethrin poisoning who developed four distinct patterns of bilirubin derangement. Case 1 demonstrated predominantly indirect hyperbilirubinemia consistent with hemolytic pattern; Case 2 developed hepatocellular pattern characterized by elevated aminotransferases; Case 3 exhibited a cholestatic pattern with predominant direct hyperbilirubinemia and elevated cholestatic enzymes; and Case 4 showed a mixed hepatocellular–cholestatic pattern. These four cases broaden the spectrum of hepatic manifestations associated with organophosphorus poisoning and highlight the importance of routine liver function monitoring for identifying atypical biochemical presentations and guiding clinical management [5].

Methods

Study Design: A retrospective observational case series was conducted involving four consecutive patients admitted with acute organophosphorus poisoning following ingestion of a chlorpyrifos–cypermethrin formulation who developed hyperbilirubinemia during the study period. Each patient demonstrated a distinct pattern of bilirubin derangement and was managed according to institutional treatment protocols. Clinical presentation, laboratory findings, treatment, serial biochemical changes, and outcomes were reviewed from hospital records. All patients received standard ICU management, including atropine, pralidoxime, supportive care, and serial biochemical monitoring.

Study Period: The study included patients admitted between January 2025 and May 2026.

Study Setting: The study was carried out in the intensive care unit of a tertiary care hospital. All 4 patients received standard management including airway stabilization, atropine therapy, supportive treatment, and close biochemical monitoring.

Data Collection: Clinical, demographic, treatment, and serial laboratory data from all four cases were retrieved from hospital medical records. Particular emphasis was placed on identifying the pattern of bilirubin derangement (hemolytic, hepatocellular, cholestatic, or mixed hepatocellular–cholestatic) using serial biochemical parameters and clinical findings.

Inclusion Criteria

- Patients aged 18 years or older.
- Confirmed acute organophosphorus poisoning due to chlorpyrifos–cypermethrin ingestion based on clinical features and markedly reduced serum cholinesterase levels.
- Availability of serial liver function tests, including bilirubin fractions (total, direct, and indirect).
- Complete clinical records documenting treatment and hospital outcome.
- Patients admitted during the study period with sufficient biochemical follow-up to evaluate the mechanism of bilirubin derangement.

Exclusion Criteria

- Pre-existing chronic liver disease or biliary obstruction.
- Known hemolytic disorders unrelated to organophosphorus poisoning.
- Viral hepatitis or other concurrent causes of acute liver injury.
- Incomplete clinical or laboratory records.

Classification of Bilirubin Derangement Patterns: For descriptive analysis, patients were categorized according to the predominant pattern of bilirubin derangement observed during hospitalization. A predominantly hemolytic pattern was defined as indirect hyperbilirubinemia without significant elevation of hepatocellular or cholestatic enzymes and was considered suggestive rather than definitive in the absence of specific hemolysis markers. A hepatocellular pattern was defined as predominant aminotransferase elevation with relatively lesser cholestatic enzyme elevation. A cholestatic pattern was defined as predominantly conjugated hyperbilirubinemia associated with elevated alkaline phosphatase and/or gamma-glutamyl transferase with minimal aminotransferase elevation. A mixed pattern was defined as the simultaneous presence of clinically significant aminotransferase and cholestatic enzyme elevations associated with conjugated hyperbilirubinemia.

Statistical Analysis: Given the descriptive nature of the study and small sample size of this four-patient case series, no inferential stastical analysis was performed. Serial clinical and biochemical trends were summarized descriptively.

Ethical Considerations: Patient confidentiality was maintained by anonymizing identifying information. The study was conducted in accordance with institutional ethical principles and approval.

Results

Case 1: Hemolytic Biochemical Pattern

Clinical Presentation: A 28-year-old male presented with alleged suicidal ingestion of a chlorpyrifos–cypermethrin formulation. He consumed approximately 100–120 mL of the pesticide and was brought to the emergency department within 3 hours of ingestion. On arrival, he had excessive salivation, vomiting, miosis, generalized fasciculations, and bradycardia. Serum cholinesterase was markedly reduced, confirming severe organophosphorus poisoning.

After consuming cypermethrin and chlorpyrifos, a 28-year-old man had cholinergic symptoms. Organophosphorus toxicity was confirmed by a significant decrease in serum cholinesterase levels. Total bilirubin was found to be 4.19 mg/dL in the initial liver function test, with indirect bilirubin making up 3.70 mg/dL. There was just 0.49 mg/dL of direct bilirubin. Throughout the hospital stay, AST and ALT readings stayed within normal ranges. Total bilirubin improved over time, from 4.19 mg/dL to 1.67 mg/dL, according to serial monitoring. Instead of primary hepatic damage, the prevalence of indirect bilirubin in the absence of transaminase increase suggested a hemolytic process.

CBC study showed neutrophilia, lymphopenia, thrombocytopenia, and increasing leukocytosis (17,020 to 33,800 cells/cumm). There was a significant decrease in serum cholinesterase (459 U/L).

Table 1: Comparison of Liver Function Test Parameters

Parameter	13/05/2026	22/05/2026	27/05/2026	Reference Range	Trend
Total Bilirubin (mg/dL)	4.19	2.43	1.67	0.2–1.2	↓ Improving
Direct Bilirubin (mg/dL)	0.49	1.28	0.86	0.0–0.3	↓ Improving
Indirect Bilirubin (mg/dL)	3.70	1.15	0.81	0.2–1.0	↓ Improving
SGPT/ALT (U/L)	18.1	31.2	28.9	10–49	Normal
SGOT/AST (U/L)	17.1	16.1	29.5	0–34	Normal
Alkaline Phosphatase (U/L)	41	76	71	68–306	Normalized
Total Protein (g/dL)	8.0	5.4	6.0	6.0–8.2	Initially decreased, improved
Albumin (g/dL)	4.8	4.0	3.1	3.5–5.2	↓ Declining
Globulin (g/dL)	3.2	1.4	2.9	2.3–3.5	Improved
A/G Ratio	1.50	2.86	1.07	0.9–2.0	Returned toward normal

Interpretation: Serial liver function tests demonstrated a progressive decline in total and indirect bilirubin with persistently normal transaminases, suggesting predominantly hemolytic pattern rather than primary hepatocellular injury.

Outcome: The patient responded well to atropine, pralidoxime, and supportive care. He showed complete clinical recovery and was discharged in stable condition after normalization of cholinergic symptoms.

Case 2: Hepatocellular Biochemical injury Pattern

Clinical Presentation: A middle-aged female presented after intentional ingestion of approximately 80–100 mL of chlorpyrifos–cypermethrin pesticide. She reached the hospital about 5 hours after exposure with profuse salivation, respiratory distress, miosis, and altered sensorium requiring ICU admission.

The second patient presented with a similar cholinergic syndrome and reduced serum cholinesterase levels. Initial bilirubin levels showed total bilirubin of 2.87 mg/dL, direct bilirubin of 0.79 mg/dL, and indirect bilirubin of 2.08 mg/dL.

Unlike Case 1, serial monitoring demonstrated progressive elevation of AST and ALT levels from 29.6 U/L and 20.2 U/L to 83.1 U/L and 65.6 U/L, respectively. Alkaline phosphatase increased from 72 U/L to 108 U/L. These findings were suggestive

of hepatocellular biochemical injury pattern secondary to organophosphorus exposure.

Total bilirubin gradually improved to 1.15 mg/dL despite rising transaminases. Protein abnormalities included decreased albumin levels and normalization of the albumin-globulin ratio during recovery.

Table 2: Comparative Liver Function Test Results

Parameter	Report 1	Report	Change
Total Bilirubin (mg/dL)	2.87	1.15	↓ Improved
Direct Bilirubin (mg/dL)	0.79	0.74	↓ Slight Improvement
Indirect Bilirubin (mg/dL)	2.08	0.41	↓ Marked Improvement
SGPT/ALT (U/L)	20.2	65.6	↑ Increased
SGOT/AST (U/L)	29.6	83.1	↑ Increased
Alkaline Phosphatase (U/L)	72.0	108.0	↑ Increased
Total Protein (g/dL)	4.7	6.8	↑ Improved
Albumin (g/dL)	3.9	3.3	↓ Decreased
Globulin (g/dL)	0.80	3.50	↑ Increased
A/G Ratio	4.88	0.94	↓ Normalized

Interpretation: Although bilirubin levels progressively declined, AST, ALT, and alkaline phosphatase increased during follow-up, indicating transient hepatocellular injury pattern caused by organophosphorus poisoning. The discordant trend of improving bilirubin with a transient rise in aminotransferases suggests evolving hepatocellular biochemical injury during clinical recovery.

Outcome: The patient improved clinically with standard treatment including atropine, oximes, ventilatory support, and intensive monitoring. Liver enzymes gradually normalized during follow-up, and she was discharged without residual hepatic dysfunction.

Comparative Findings: The most notable difference between the two cases was the mechanism of bilirubin elevation. Case 1 demonstrated predominantly indirect hyperbilirubinemia without hepatic enzyme abnormalities, whereas Case 2 exhibited biochemical evidence of hepatocellular injury. Both patients showed clinical improvement and normalization of bilirubin levels with treatment.

Case 3: Cholestatic Biochemical Pattern

Clinical Presentation: A 42-year-old male farmer presented after intentional ingestion of nearly 150 mL of chlorpyrifos (50%) and cypermethrin (5%). He reached the tertiary care hospital approximately 6 hours after ingestion with cholinergic manifestations including excessive salivation, bronchorrhea, fasciculations, and bradycardia. Atropine infusion and ICU admission were necessary for the patient.

Table 3: Laboratory Findings

Parameter	Day 1	Day 5	Day 10
Serum Cholinesterase (U/L)	635	1120	2680
Total Bilirubin (mg/dL)	5.12	3.42	1.82
Direct Bilirubin (mg/dL)	3.84	2.25	0.96
Indirect Bilirubin (mg/dL)	1.28	1.17	0.86
AST (U/L)	42	38	32
ALT (U/L)	48	44	36
Alkaline Phosphatase (U/L)	312	280	148
GGT (U/L)	146	118	62
Total Protein (g/dL)	6.1	6.4	6.9
Albumin (g/dL)	3.4	3.5	3.8

Interpretation: Serial biochemical monitoring demonstrated steady improvement in direct bilirubin, alkaline phosphatase, and GGT, indicating cholestatic biochemical pattern. Ultrasonography of the hepatobiliary system was normal and the relatively stable AST and ALT values suggest minimal hepatocellular necrosis, while increasing serum cholinesterase reflected recovery from organophosphorus toxicity.

Outcome: The patient showed progressive clinical improvement, recovered without major complications, and was discharged after normalization of liver function and cholinesterase levels.

Case 4: Mixed Hepatocellular–Cholestatic Biochemical Pattern

Clinical Presentation

A 25-year-old female accidentally ingested approximately 70–80 mL of chlorpyrifos–cypermethrin pesticide. She reached the hospital around 2 hours after ingestion with severe respiratory distress, excessive secretions, and depressed consciousness, requiring endotracheal intubation and mechanical ventilation.

Table 4: Laboratory Findings

Parameter	Day 1	Day 6	Day 12
Serum Cholinesterase (U/L)	421	975	2410
Total Bilirubin (mg/dL)	4.78	2.98	1.54
Direct Bilirubin (mg/dL)	2.41	1.63	0.71
Indirect Bilirubin (mg/dL)	2.37	1.35	0.83
AST (U/L)	132	98	42
ALT (U/L)	156	120	51
Alkaline Phosphatase (U/L)	228	184	118
Total Protein (g/dL)	5.8	6.1	6.8
Albumin (g/dL)	3.1	3.3	3.7
Globulin (g/dL)	2.7	2.8	3.1

Interpretation: The serial liver function profile demonstrated simultaneous improvement in bilirubin fractions and liver enzymes, consistent with mixed hepatocellular–cholestatic biochemical pattern. Increasing serum proteins and albumin further reflected restoration of hepatic synthetic function during treatment.

Outcome: The patient required mechanical ventilation for 48 hours but responded well to atropine, pralidoxime, and supportive intensive care. She was successfully extubated, made a complete clinical recovery, and was discharged in stable condition without residual neurological or hepatic sequelae.

Discussion

This case series describes four distinct biochemical patterns of bilirubin derangement following chlorpyrifos–cypermethrin poisoning: predominantly indirect hyperbilirubinemia suggestive of a hemolytic pattern, hepatocellular enzyme elevation, cholestatic biochemical abnormality, and a mixed hepatocellular–cholestatic pattern. Previous clinical studies have demonstrated associations between biochemical abnormalities including bilirubin and liver enzyme elevation, and the severity of acute organophosphorus poisoning [7]. The findings suggest that hepatic and bilirubin abnormalities in acute pesticide poisoning may extend beyond the classical cholinergic manifestations. The biochemical profile of the first patient was in line with hemolytic hyperbilirubinemia. When combined with normal AST and ALT readings, The predominance of indirect bilirubin in the absence of significant aminotransferase elevation suggested a predominantly prehepatic or hemolytic pattern; however, definitive hemolysis could not be established in the absence of dedicated hemolysis markers. Organophosphorus chemicals have been proven in experiments to cause lipid peroxidation and oxidative stress in erythrocyte membranes. Such damage could make membranes more brittle and encourage hemolysis. Although organophosphorus poisoning seldom results in overt hemolysis, the biochemical pattern may be explained by subclinical erythrocyte damage [6].

The second patient's bilirubin concentrations improved, but their AST and ALT levels gradually increased. This pattern was suggestive of transient hepatocellular biochemical injury. Reactive oxygen species produced by the metabolism of chlorpyrifos can harm hepatocyte membranes [11], interfere with mitochondrial activity, and cause inflammatory reactions. Studies on animals have shown that exposure to chlorpyrifos causes oxidative damage, lipid alteration, and hepatocellular degeneration [12]. Tczhe transient rise in aminotransferases suggests ongoing hepatocellular biochemical injury during the early recovery phase. By demonstrating cholestatic and mixed hepatocellular–cholestatic damage patterns, Cases 3 and 4 significantly broaden the range of hepatic involvement. In these situations, elevated levels of alkaline phosphatase and direct bilirubin indicate compromised hepatobiliary transport and biliary excretion [4].

The significant drop in serum cholinesterase levels was another important discovery. Measuring cholinesterase is still essential for diagnosing and determining the severity of organophosphorus poisoning [8]. All four patients had marked serum cholinesterase inhibition with associated biochemical abnormalities at presentation, followed by progressive normalization during recovery. Laboratory parameters gradually returned to normal after recovery. Leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia were among the haematological abnormalities found in Case 1. These results most likely represent stress reactions and systemic inflammatory activation brought on by acute poisoning. Previous toxicological

investigations have documented similar haematological alterations [9].

These findings are especially relevant because severe hyperbilirubinemia in chlorpyrifos poisoning is uncommon. While bilirubin abnormalities receive little attention, the majority of published papers concentrate on neurological and pulmonary consequences. The current cases raise the possibility that hyperbilirubinemia is an underappreciated sign of organophosphorus toxicity. Differentiating between hepatocellular and hemolytic processes has clinical implications. While hepatocellular injury requires close observation of liver enzymes and hepatic function, hemolytic hyperbilirubinemia may need assessment for signs of red cell death. Ignoring these trends could lead to pointless tests or a delayed diagnosis [10].

This report's tiny sample size is its main drawback. However, the disparate metabolic patterns found offer important information about the varied hepatic involvement in organophosphorus poisoning. To ascertain the prevalence, prognostic importance, and pathophysiological basis of these atypical symptoms, larger prospective investigations are required. Significant exposure to organophosphorus was confirmed by a consistent result in all cases: significantly lower serum cholinesterase levels. Clinical recovery and rising cholinesterase activity were correlated with improvements in bilirubin levels during follow-up. These findings highlight how crucial it is to regularly evaluate liver function in people who have been poisoned. Atypical bilirubin abnormalities can help avoid misdiagnosis and enable prompt management. The absence of specific hemolysis markers such as lactate dehydrogenase, reticulocyte count, haptoglobin, and peripheral smear findings limited the definitive characterization of the predominantly indirect hyperbilirubinemia observed in one patient. To better understand the frequency and mechanisms of hepatic dysfunction in chlorpyrifos exposure, larger prospective investigations are necessary.

Conclusion

This case series demonstrates the wide range of bilirubin abnormalities that can develop after cypermethrin and chlorpyrifos intoxication. Patients may exhibit predominantly indirect hyperbilirubunemia suggestive of a hemolytic, as well as hepatocellular, cholestatic, or mixed types of hyperbilirubinemia in addition to traditional cholinergic symptoms. Serial liver function monitoring and serum cholinesterase measurements were useful for characterization and followup. The results imply that the haematological and hepatic consequences of organophosphorus poisoning are more varied than previously thought. In patients with organophosphorus toxicity, clinicians should think about routinely evaluating liver function, especially if there are unexplained biochemical abnormalities or jaundice. To determine the prevalence, causes, and prognostic importance of these atypical symptoms, more multicenter research is required.

Conflict of Interest: The authors declare no conflict of interest.

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